REMARKS

Claims 27-30 have been amended. Claims 27-30 are pending in the present application.

It is respectfully submitted that the present amendment presents no new issues or new matter and places this case in condition for allowance. Reconsideration of the application in view of the above amendments and the following remarks is requested.

I. Claim Objections

Claims 29 and 30 stand objected to because the claims recite that the cell is the "host cell of NRRL 30747" and it would be remedial to recite that the cell is the "host cell deposited under NRRL 30747".

Applicant has amended claims 29 and 30 to recite the "host cell deposited under NRRL 30747" according to the Examiner's suggestion.

For the foregoing reason, Applicant submits that the objections have been overcome and respectfully request withdrawal of the objections.

II. The Rejection of Claims 27-30 Under the Judicially Created Doctrine of Obviousness-Type Double Patenting

Claims 27-30 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 15 and 16 of U.S. Patent No. 6,893,839. The Office Action stated:

> Although the conflicting claims are not identical, they are not patentably distinct from each other because the cited claims of the instant invention are generic to all that is recited in claims 1, 2, 15 and 16 of U.S. 6,893,839. That is, the cited claims of U.S. 6,893,839 anticipate and fall entirely within the scope of the rejected claims of the instant application. Specifically, the instant claims and U.S. 6,893,839 claims recite a *Fusarium venenatum* cell that is specifically ATCC 20334 and its use for the production of heterologous proteins.

Applicant submits a terminal disclaimer in compliance with 37 CFR 1.3219(c). Applicant suggests that the terminal disclaimer should be limited to claims 29 and 30 based on the new presented claims.

For the foregoing reason, Applicant submits that the claims overcome this rejection and respectfully request reconsideration and withdrawal of the rejection.

III. The Rejection of Claims 27-28 under 35 U.S.C. § 112, First Paragraph

Claims 27-28 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The Office Action stated:

> An adequate written description of the invention defined by the claims requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is the knowledge in the prior art and/or a description as to the availability of a representative number of species of claimed nucleic acid sequences. In the instant case, applicants have only demonstrated a single isolate that is non-toxic, non-toxigenic, and non-pathogenic. The prior art teaches that these cells encode toxic proteins naturally. As well, the prior art does not teach other isolates of *Fusarium venenatum* or any other naturally occurring cells that meet the broad definition of potential host strains are non-toxic, non-toxigenic and non-pathogenic. Furthermore, applicants have not demonstrated that variance of this strain would result in a cell that is functionally similar to disclosed ATCC 20334. As well, the specification fails to convey the relevant identifying characteristics of ATCC 20334 such that the structural requirements of the cell can be envisioned. Therefore, the relationship between structure and function is unclear as neither applicant nor the prior art provide a correlation between the ATCC 20334 and the ability to be non-toxic, non-toxigenic and non-pathogenic in order to produce heterologous proteins. Given the large size and diverse nature of the potential cells and the inability to determine which will also possess the recited characteristics, it is concluded that the invention must be empirically determined. In an unpredictable art, the disclosure of ATCC 20334 or NRRL 30747 would not represent to the skilled artisan a representative number of species sufficient to show applicants were in possession of claimed genus.

This rejection is respectfully traversed.

The Office alleges that the specification fails to convey the relevant identifying characteristics of *Fusarium venenatum* ATCC 20334 and that the relationship between structure and function is unclear as neither applicant nor the prior art provide a correlation between *Fusarium venenatum* ATCC 20334 and the ability to be non-toxic, non-toxigenic, and non-pathogenic in order to produce heterologous proteins. Applicant disagrees with these assertions.

It is well settled that a patent need not teach and preferably omits what is well known in the art. Spectra-Physics Inc. v. Coherent Inc., 3 U.S.P.Q.2d 1737 (Fed. Cir. 1987).

Applicant submits that the identifying characteristics of *Fusarium* strain A3/5 (ATCC PTA-2684 = ATCC 20334 = NRRL 26139 = IMI 145425 = NRRL 30747) have been well known in the art prior to the priority date of June 30, 1994 of the instant invention and consequently Applicant need not teach and preferably can omit what is well known in the art. However, Applicant provides relevant identifying characteristics on page 5, line 24 to page 6, lines 6, of the

specification.

The term "identifying characteristics" is well known in the art and refers to the growth and morphological properties of a strain. The Office should note that the term "identifying characteristics" already appears in dozens of issued U.S. patents which are directed to strains. Thus, there clearly is a precedent for this type of language in U.S. patent claims. Since the Office has objected to the term "identifying characteristics", Applicant has amended claims 27 and 28 to recite the following substitute language: "wherein the non-toxic, non-toxigenic, and non-pathogenic *Fusarium venenatum* host cell has the morphological and growth characteristics ... of *Fusarium venenatum* deposited under NRRL 30747". Applicant's contention that the identifying characteristics of *Fusarium* strain A3/5 have been well known in the art prior to the instant priority date is supported by the following facts.

Fusarium strain A3/5 has been known since the 1970's and has been the subject of numerous published papers and patents, covering especially its use as a protein source for human consumption. Several of these publications are discussed herein. The development of mycoprotein from *Fusarium* strain A3/5 has been reviewed by Edelman *et al.*, 1983, *Nutr. Abstr. Rev. Clin. Nutr.* 53: 471-480 (attached); and Trinci, 1992, *Mycol. Res.* 96: 1-13 (attached). *Fusarium* strain A3/5 was first investigated as a potential protein source for human consumption during the late 1960s by the British company Rank Hovis McDougall (RHM). RHM selected *Fusarium* strain A3/5 for further product development after 3 years of screening (Anderson and Solomons, 1984, Primary metabolism and biomass production from *Fusarium*. *In*: Moss MO, Smith JE (eds), The applied mycology of *Fusarium*. Cambridge University Press, Cambridge, pp 231–250 [attached]). In order to bring mycoprotein from *Fusarium* strain A3/5 onto the market, it was necessary for RHM to invest 12 years in researching the safety of the organism and of the final product, making mycoprotein the most carefully tested food product on the European market (Edelman *et al.*, 1983, *supra*; Anderson and Solomons, 1984, *supra*; Solomons, 1986, Microbial proteins and regulatory clearance for RHM myco-protein. In: Moo-Young M, Gregory KF (eds) Microbial biomass proteins. Elsevier, London, pp 19–26 [attached]; Solomons, 1987, Myco-Protein: Safety Evaluation of a Novel Food, *Arch. Toxicol. Suppl.* 11: 191-193 [attached]). Mycoprotein produced from *Fusarium* strain A3/5 was approved by the Ministry of Agriculture, Fisheries and Food (MAFF) for sale in the United Kingdom in 1984.

Claims 27 and 28 recite in part: "wherein the non-toxic, non-toxigenic, and non-pathogenic *Fusarium venenatum* host cell has the morphological and growth characteristics ... of *Fusarium venenatum* deposited under NRRL 30747". The issue in question is whether the prior

art describes the morphological and growth characteristics of *Fusarium venenatum* strain A3/5 deposited under NRRL 30747. Applicant asserts that the morphological and growth characteristics of *Fusarium* strain A3/5 were well known in the art prior to the priority date of the instant invention. There are several published references that describe the identifying characteristics of morphology and growth for *Fusarium* strain A3/5. Several of these references are discussed below.

U.S. Patent No. 3,937,654, which issued on February 10, 1976, discloses the growth and morphological characteristics of *Fusarium* strain A3/5 (ATCC PTA-2684 = ATCC 20334 = NRRL 26139 = IMI 145425 = NRRL 30747) on column 2, lines 5-44 (attached). U.S. Patent No. 3,937,654 is referenced in the ATCC catalogue for strain ATCC 20334 (attached). GB Serial No. 1,346,061 describes and claims *Fusarium* strain IMI 145425 and also discloses growth and morphological characteristics of the strain (attached). Anderson and Solomons, 1984, *supra*, and Trinci, 1992, *supra*, disclose the growth characteristics of *Fusarium* strain A3/5 (both attached). Nirenberg, 1995, *Mycopathologia* 129: 131-141 (attached), describe the morphological differentiation of *Fusarium sambucinum* Funkel sensu stricto, *F. torulosum* (Berk. & Curt.) Nirenberg comb. Nov. and *Fusarium venenatum* Nirenberg sp. nov. While the Nirenberg article published after the filing date, it was received September 8, 2003 and accepted in revised form January 10, 1995, and clearly demonstrates the state of art at the time of the filing of the instant invention. Applicant also describes specific growth and morphological characteristics of this species on page 5, line 24 to page 6, line 3, of the instant specification.

These published references in combination with Applicant's specification convey the relevant identifying characteristics, *i.e.*, morphological and growth characteristics, of *Fusarium venenatum* deposited under NRRL 30747 to one skilled in the art. It is well settled that a patent need not teach and preferably omits what is well known in the art. Spectra-Physics Inc., 3 U.S.P.Q.2d at 1737.

Claims 27 and 28 also recite in part: "wherein the non-toxic, non-toxigenic, and non-pathogenic *Fusarium venenatum* host cell has ... the non-toxic, non-toxigenic, and non-pathogenic properties of *Fusarium venenatum* deposited under NRRL 30747". Another issue in question is whether the prior art describes the non-toxic, non-toxigenic, and non-pathogenic properties of *Fusarium venenatum* deposited under NRRL 30747. Applicant also asserts that the non-toxic, non-toxigenic, and non-pathogenic properties of *Fusarium* strain A3/5 were well known in the art prior to the priority date of the instant invention. Applicant defines the terms "non-toxic", "non-toxigenic", "non-pathogenic" on page 5, lines 3-16, of the specification. There

are several published references that describe the non-toxic, non-toxigenic, and non-pathogenic properties for *Fusarium* strain A3/5 and the toxic, toxigenic, and pathogenic properties of other strains of *Fusarium*. Several of these references are discussed below.

Solomons, 1986, *supra*, and Solomons, 1987, *supra*, reported on the extensive safety testing undertaken for mycoprotein from *Fusarium* strain A3/5 and that testing for a range of mycotoxins all proved negative, even where detection levels were as low as 1 µg per kg. Solomons' results have been recently confirmed by O'Donnell *et al.*, 1998, *Fungal Genetics and Biology* 23: 57-67 (attached). Solomons, 1986, *supra*, references the U.S. Food & Drug Administration, 1984, Toxicological Principles for the Safety Assessment of Direct Food Additives & Additives used in Food, FDA, Washington, D.C. A copy of the current Table of Currents is attached. The Toxicological Principles outline the toxicity studies that are required to establish the safety of a food additive. Udall *et al.*, 1984, *The American Journal of Clinical Nutrition* 40: 285-292, reports on the tolerance and nutritional value of *Fusarium* strain A3/5 mycoprotein (attached).

ApSimon *et al.*, 1990, *Pure & Appl. Chem.* 62: 1339-1346 (attached), describe the detection, determination, and variety of mycotoxins, *e.g.*, trichothecenes, enniatins, and fusarins, produced by *Fusarium* species. Marasa *et al.*, 1984, *Toxigenic Fusarium Species: Identity and Mycotoxicology*, Pennsylvania State University, University Park, describe the identity and mycotoxicology of *Fusarium* species. The mycotoxins trichothecenes, enniatins, and fusarins are of particular interest when discussing *Fusarium venenatum* strains since these mycotoxins have been shown to be produced by other *Fusarium* species. Several of the published references directed to trichothecenes, enniatins, and fusarins are discussed below.

The chemistry and genetics of trichothecene biosynthesis in *Fusarium* species is described by Desjardins *et al.*, 1993, *Microbiol. Rev.* 57: 595-604 (attached). Trichothecenes are sesquiterpene epoxides which are named after the fungus *Trichothecium roseum* from which the first trichothecene was isolated. The trichothecenes T-2 toxin, diacetoxyscirpenol, and deoxynivalenol are most commonly found in agricultural commodities infected with *Fusarium* species. Desjardins *et al.*, 1993, *supra*, disclose that trichothecenes are produced by a sequence of oxygenations, isomerizations, cyclizations, and esterifications leading from trichodiene, which is produced from the cyclization of *trans*, *trans*-farnesyl pyrophosphate by the enzyme trichodiene synthase. The trichodiene synthase gene (*tri5* or *tox5*) has been cloned from *Fusarium sporotrichioides* (Hohn and Beremand, 1989, *Gene* 79: 131-138); *Gibberella pulicaris* (Hohn and Desjardins, 1992, *Molecular Plant-Microbe Interactions* 5: 249-256); *Gibberella zeae*

(Proctor *et al.*, 1995, *Molecular Plant-Microbe Interactions* 4: 593-601); *Myrothecium roridin* (Trapp, *et al.*, 1995, *Journal of Cellular Biochemistry Supplement* 19B: 154); and *Fusarium poae* (Fekete *et al.*, 1997, *Mycopathologia* 138: 91-97). Desjardins *et al.* also disclose that *Tri5* mutants of *Gibberella pulicaris* (Hohn and Desjardins, 1992, *supra*) have been generated which do not produce trichothecenes. ApSimon *et al.*, 1990, *supra*, describe the detection and determination of trichothecenes, produced by *Fusarium* species (attached).

Enniatins are cyclohexadepsipeptide phytotoxins with ionophoretic properties produced by various species of actinomycetes and filamentous fungi, particularly strains of *Fusarium* (Walton, 1990, *Biochemistry of Peptide Antibiotics*, H. Kleinkauf and H. von Dohren, editors, W. de Gruytre, Berlin, pp. 179-203), and also exhibit entomopathogenic properties (Grove and Pople, 1980, *Mycopathologia* 70: 103-105). Kleinkauf and von Döhren, 1990, *Eur. J. Biochem.* 192: 1-15 (attached), and Billich and Zocher, 1990, *In* Kleinkauf, H., von Döhren (eds.), *Biochemistry of Peptide Antibiotics*, Berlin, W. de Gruyler, pp. 57-79 (attached) describe the biosynthesis of enniatins catalyzed by enniatin synthetase, which is a large multifunctional enzyme that has all the essential functions for assembling enniatins from their primary precursors, *i.e.*, D-2-hydroxyisovaleric acid, a branched chain L-amino acid (*e.g.*, valine, leucine, isoleucine), S-adenosylmethionine, and ATP. The precursors (D-2-hydroxyisovaleric acid and branched chain L-amino acid) are activated as thioesters. Covalently bound substrate amino acid residues are methylated under the consumption of S-adenosylmethionine. Then peptide bond formation and cyclization reactions occur. Enniatins are composed of alternating D-2-hydroxyisovaleric acid residues and L-amino acids or N-methyl-L-amino acids to form an 18-membered cyclic structure and may contain more than one species of amino acid. An enniatin synthetase gene (*esyn1*) has been cloned from *Fusarium scirpi* (Haese *et al.*, 1993, *Molecular Microbiology* 7: 905-914 [attached]). ApSimon *et al.*, 1990, *supra*, describe the detection and determination of enniatins, produced by *Fusarium* species (attached).

Fusarins have been isolated from a number of *Fusarium* species including *Fusarium venenatum* (Gelderblom *et al.*, 1984, *J. Chem. Soc. Chem. Commun.* 122-124 [attached]). These compounds are potent mycotoxins. Their biosynthesis has been studied by using classical feeding experiments with ^{13}C-labelled acetates (Steyn and Vleggaar, 1985, *J. Chem. Soc. Chem. Commun.* 1189-1191 [attached]). These experiments showed that seven intact acetates make the polyunsaturated side chain and two of the pyrrolidin-2-one carbon atoms. The other four carbon atoms were also labeled by acetate, but label scrambling and a low level of incorporation suggested that these carbon atoms were derived from a Krebs cycle intermediate, possibly

aspartate, oxaloacetate or their derivatives. The four side-chain carbon atoms are derived from S-adenosylmethionine, as is the methoxygroup in the methyl ester. ApSimon *et al.*, 1990, *supra*, describe the detection and determination of fusarins, produced by *Fusarium* species (attached).

These published references in combination with Applicant's specification provide a correlation between *Fusarium venenatum* ATCC 20334 and the ability to be non-toxic, non-toxigenic, and non-pathogenic to one skilled in the art to understand the identifying characteristics of a *Fusarium venenatum* strain that is non-toxic, non-toxigenic, and non-pathogenic (*e.g.*, NRRL 30747). It is well settled that a patent need not teach and preferably omits what is well known in the art. Spectra-Physics Inc., 3 U.S.P.Q.2d at 1737.

The Office suggests that the relationship between structure and function is unclear as neither applicant nor the prior art provide a correlation between *Fusarium venenatum* ATCC 20334 and the ability to be non-toxic, non-toxigenic, and non-pathogenic. This assertion has no support as evidenced by the discussion of the prior art above. It is abundantly clear that *Fusarium* strain A3/5 is non-toxic, non-toxigenic, and non-pathogenic simply because the strain does not produce mycotoxins. Consequently, the prior art does provide an explanation of the correlation between *Fusarium venenatum* ATCC 20334 and the ability to be non-toxic, non-toxigenic, and non-pathogenic, as described above.

The Office alleges that the prior art does not teach other isolates of *Fusarium venenatum* that meet the broad definition of potential host strains that are non-toxic, non-toxigenic, and non-pathogenic and Applicant has not demonstrated that variance of this strain would result in a cell that is functionally similar to disclosed ATCC 20334.

The Examiner's desire for other isolates of *Fusarium venenatum* that meet the definition of potential host strains that are non-toxic, non-toxigenic, and non-pathogenic is apparently derived from University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997), which the Examiner characterized as holding what is required for an adequate written description "is the knowledge in the prior art and/or a description as to the availability of a representative number of species of claimed nucleic acid sequences". Applicant submits that the Office's reliance on Lilly is inappropriate. The claims in Lilly were to a chemical compound (cDNA encoding human insulin), yet neither the claims nor the specification defined the structure of the claimed compound. *See* 119 F.3d at 1567, 43 USPQ2d at 1404-1405 ("[T]he definition of the claimed microorganism is one that requires human insulin-encoding cDNA ... [T]here is no further information in the patent pertaining to that cDNA's relevant structural or physical characteristics; in other words, it thus does not describe human insulin cDNA.") Here, by

contrast, the claims define an isolated non-toxic, non-toxigenic, and non-pathogenic *Fusarium venenatum* host cell comprising a nucleic acid sequence encoding a heterologous protein, wherein the non-toxic, non-toxigenic, and non-pathogenic *Fusarium venenatum* host cell has the identifying characteristics of *Fusarium venenatum* deposited under NRRL 30747 and a method for producing a heterologous protein using such a host strain. There is no compound involved, such as cDNA encoding human insulin. Consequently, the Office's reliance on Lilly is misplaced.

"The function of the description requirement is to ensure that the inventor had possession of, as of the filing date of the application relied upon, the specific subject matter later claimed by him ... It is not necessary that the application describe the claim limitations exactly, but only so clearly that one having ordinary skill in the pertinent art would recognize from the disclosure that appellants invented processes including those limitations." In re Herschler, 591 F.2d 693, 700, 200 USPQ 711, 717 (CCPA 1979). In the instant case, although the specification exemplifies only *Fusarium venenatum* deposited under NRRL 30747 within the scope of the instant claims, Applicant's disclosure and the knowledge in the prior art is adequate to show that Applicant was in possession of a non-toxic, non-toxigenic, and non-pathogenic *Fusarium venenatum* host cell having the morphological and growth characteristics and the non-toxic, non-toxigenic, and non-pathogenic properties of *Fusarium venenatum* deposited under NRRL 30747, as claimed. The claim language "wherein the non-toxic, non-toxigenic, and non-pathogenic *Fusarium venenatum* host cell has the morphological and growth characteristics and the non-toxic, non-toxigenic, and non-pathogenic properties of *Fusarium venenatum* deposited under NRRL 30747" is intended to prevent potential infringers from mutating a toxic, toxigenic, and pathogenic *Fusarium venenatum* strain so it is non-toxic, non-toxigenic, and non-pathogenic. It was within the skill in the art at the time of the filing of the instant application to produce by classical mutagenesis and screen for a mutant of toxic, toxigenic, and pathogenic *Fusarium venenatum* strains that is non-toxic, non-toxigenic, and non-pathogenic and having the identifying characteristics of *Fusarium venenatum* deposited under NRRL 30747. It was also within the skill in the art at the time of the filing of the instant application to construct a disruption cassette directed to a gene involved in the biosynthesis of a mycotoxin. See, for example, Hohn and Beremand, 1989, Isolation and nucleotide sequence of a sesquiterpene cyclase gene from the trichothecene-producing fungus *Fusarium sporotrichioides*, *Gene* 79: 131-138 (attached); Hohn and Desjardins, 1992, Isolation and gene disruption of the *Tox5* gene encoding trichodiene synthase in *Gibberella pulicaris*, *Molecular Plant-Microbe Interactions* 5: 249-256 (attached); Haese *et al.*, 1993, Molecular characterization of the eniatin synthetase

gene encoding a multifunctional enzyme catalyzing N-methyldepsipeptide formation in *Fusarium scirpi*, *Molecular Microbiology* 7: 905-914 (attached). It was also within the skill in the art at the time of the filing of the instant application to produce a non-toxic, non-toxigenic, and non-pathogenic *Fusarium venenatum* strain having the identifying characteristics of *Fusarium venenatum* deposited under NRRL 30747 by using a combination of the above approaches.

For the foregoing reasons, Applicant submits that this rejection under 35 U.S.C. § 112 has been overcome and respectfully requests withdrawal of the rejection.

IV. Conclusion

In view of the above, it is respectfully submitted that all claims are in condition for allowance. Early action to that end is respectfully requested. The Examiner is hereby invited to contact the undersigned by telephone if there are any questions concerning this amendment or application.

Respectfully submitted,

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